Remarks

Claims 1-29 are pending. Claims 1-12, 14 and 17-29 are cancelled without prejudice to the filing of a divisional application. Reconsideration of claims 13, 15 and 16 is respectfully requested based on the following remarks.

Response to the section 103(a) rejection

Claims 13, 15 and 16 are rejected under 35 U.S.C. 103(a) as allegedly rendered obvious by Garcia et al. (1997), *Cell Growth and Differentiation* 8: 1267-1276 ("Garcia") and Takemoto et al. (1997), *PNAS USA* 94: 13897-13902 ("Takemoto"), further in view of University of Michigan Medical School (1997), *Prec. Ann. Meet. Assoc. Cancer Res.* 38: A375 (UMich Abstract). Applicants respectfully traverse the rejection.

To support a case of *prima facie* obviousness, a combination of references must: (1) suggest to those of ordinary skill in the art that they should make the claimed invention, and (2) reveal to those of ordinary skill in the art that they would have a reasonable expectation of success. In re Vaeck, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art and not in the applicant's disclosure. In re Dow Chemical Company, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Here, there is nothing in Garcia, Takemoto or the UMich abstract that would motivate one of ordinary skill in the art to combine the teachings of these references to produce the presently claimed invention, or which would provide a reasonable expectation of success that the claimed methods could be practiced.

Garcia reports an increased STAT-3 DNA binding activity in breast cancer cell lines or rat fibroblast which are induced to undergo transformation. The Examiner alleges that Garcia shows a correlation between STAT-3 activation and metastatic potential. In fact, Garcia states that "constitutive activation of Stat3 is a frequent event in breast carcinoma cells" which is "*consistent* with a role for Stat3 signaling in breast cancer progression" (Garcia, pg. 1274, col. 1, 1st para, emphasis added). The only *correlation* recognized by Garcia is that between STAT-3 activation and transformation of cancer cells by src (Garcia, pg. 1274, col. 1, 2nd para.). While transformation must take place for ultimate metastasis of a cell, it is clear from the evidence presented in the response filed July 30, 2002 that a transformational event is not always indicative of future metastatic activity. In other words,

transformation is a necessary but not universally sufficient event for metastasis. One of ordinary skill in the art would therefore not recognize from the teachings of Garcia that src-induced transformation, as characterized by STAT-3 activation, heralds the eventual metastasis of the transformed cell. This connection was first made in Applicant's specification.

Likewise, Takemoto does not correlate STAT-3 activation with metastatic potential, but rather discusses STAT-3 activation only in terms of cellular transformation; see the response filed July 30, 2002. Indeed, it appears that the Examiner cites Takemoto only for the proposition that STAT-3 can be sampled in cancer patients (see Detailed Action, pg. 6). Thus, one of ordinary skill in the art would not consider the evidence that STAT-3 activation is correlated with cellular transformation, as presented in Garcia and Takemoto, to mean that STAT-3 activation is also correlated with metastatic potential. Indeed, from the withdrawal of the previous obviousness rejection of the present claims over Garcia and Takemoto alone (see Detailed Action, pg. 5, 2nd para.), the examiner admits that the combination of Garcia and Takemoto does not reasonably suggest to one skilled in the art that activated STAT-3 can successfully be used as an indicator of tumor metastatic potential.

In an attempt to cure the deficiencies of Garcia and Takemoto, the Examiner now alleges that the UMich abstract shows metastatic (as opposed to merely transformed) breast cancer cells have high levels of activated STAT-3. The UMich abstract discloses that ten human breast cancer cell lines were isolated from both primary and metastatic tumors, and states that "several" of these cells lines have high levels of activated STAT-3. However, the UMich abstract does not identify *which* cell lines have the activated STAT-3. It is not clear how many of the "several" cell lines with activated STAT-3, if any, are from metastatic tumors. The UMich abstract therefore does not establish a correlation between STAT-3 activation and metastatic potential, and cannot supply the motivation lacking in Garcia and Takemoto to practice the claimed methods with any reasonable expectation of success. The 35 U.S.C. 103(a) rejection of claims 13, 15 and 16 over the cited references should therefore be withdrawn.

The Examiner cautions Applicants against countering an obvious rejection by attacking the cited references individually. However, the scope and content of each reference must be set forth before discussing the collective impact of the references on one

of ordinary skill in the art. Applicants have established that neither Garcia nor Takemoto teach that activated STAT-3 is correlated with the metastatic potential of a cancer cell. Moreover, Applicants have shown that the UMich abstract fails to associate the presence of activated STAT-3 with any particular cell line derived from metastatic cells, and thus does not establish a correlation between activated STAT-3 and metastatic potential. Absent the teachings of Applicants' disclosure, the combination of these three references would not reasonably suggest to one of ordinary skill in the art that the metastatic potential of a cancer cell can be predicted with any degree of success from the presence of activated STAT-3 in that cell.

Conclusion

Based on the foregoing, all claims are believed in condition for allowance. An early and favorable action toward that end is earnestly solicited.

Respectfully submitted,

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